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Drug allergy in patients with tuberculosis and concomitant chronic obstructive pulmonary disease

Key words: *drug allergy, pulmonary tuberculosis, chronic obstructive pulmonary disease*

Today, pulmonary tuberculosis (PTB) and chronic obstructive pulmonary disease (COPD) constitute an important medical and social problem for most countries of the world. This is due to their significant prevalence, considerable negative impact on quality of life, working capacity and mortality of the population, etc. [3, 10, 11]. Combination of these pathologies further complicates the treatment process for patients both with PTB and COPD; in particular, it affects the efficacy of therapy in the first patient population. In addition, there comes a problem of combination of PTB and COPD not only among themselves, but with allergic diseases (AD) that have already become epidemic all over the world [8, 13]. Thus, the presence of AD, especially drug allergies (DA), in patients with PTB and COPD prolongs the duration of their treatment, reduces its efficacy, decreasing the rate of cessation of bacterial shedding and healing the cavities of lung destruction, increases the incidence of ineffective therapy, PTB relapses and complications, exacerbations of COPD, formation of chronic cor pulmonale, which in general worsens the epidemic and social and economic situation associated with tuberculosis [2, 4–7].

As stated above, there are few publications in the literature of past years [1, 3–6, 9, 12, 14] concerning the influence of AD, in particular DA, on the clinical course and outcome of treatment of patients with PTB, but these studies were predominantly conducted 10–20 years before, when the prevalence of allergic conditions was lower and the course of tuberculosis was more favorable. Moreover, creation of a system of the measures aimed at timely detection, specific diagnosis, effective treatment and prevention of AD in patients with PTB and in its combination with COPD remains a relevant issue. All this will contribute to increasing the efficacy and reducing the duration of treatment for both underlying disease and comorbidities.

The aim of this study was to determine the incidence and structure of DA in patients with PTB and concomitant COPD and the influence of adverse reactions to antituberculosis agents on the results of treatment in the respective patient population.

Materials and methods

A retrospective analysis of the medical records of 331 patients with newly diagnosed PTB and concomitant COPD who were on treatment at the State Institution «National Institute of Phthisiology and Pulmonology named after F.G. Yanovsky of NAMS of Ukraine» in 2006–2016 was carried out. All patients with PTB received antituberculosis agents (ATA), as well as the COPD maintenance therapy in accordance with the current protocols. Differentiation of adverse reactions to ATA, in particular DA, was performed using the standard allergological research methods which included the collection of complaints, history of allergic disorders, physical examination of patients, and laboratory testing with allergy-causing drugs via reactions of inhibition of WBC migration and agglomeration. The results of clinical, X-ray, functional, laboratory examinations and collection of the history of allergic disorders of patients were processed and calculated using parametric and non-parametric statistical methods. While processing the results for each parameter, the mean square deviation, the arithmetic mean (M), and the standard error of the arithmetic mean (m) were calculated. The probability of the difference between the groups in which the data were distributed according to normal law was estimated using the t-test based on the Student table, but if the distribution

law was different of the normal according to U-test, – using the paired Wilcoxon-Mann-Whitney test. Data for which $p < 0.05$ were considered as statistically significant. Differences for which $p > 0.05$ were considered as a trend. The findings of examination and treatment of patients with PTB and concomitant COPD were stored, processed and computed using licensed software products of a package of mathematical and statistical methods using Microsoft Office Professional 2007, license No 43437596.

Results and discussion

The study showed that in 331 patients with PTB and concomitant COPD, 193 (58.3±2.9)% of individuals developed one or another adverse reaction to ATA. In the remaining 138 (41.7±1.7)% of patients, satisfactory tolerance to ATA was observed. Differences between parameters are significant, at $p < 0.05$. True allergic reactions (DA) to ATA were detected in 71 (21.5±2.1)% of 331 subjects. However, if we add the reactions of toxic-allergic origin which occurred in 36 (10.9±1.1)% of individuals to the cases of true allergic reactions, the overall incidence of allergic and toxic-allergic reactions increased, since they were reported in 107 (32.3±2.9)% of patients with PTB and concomitant COPD. Medical history is known to play an important role in the diagnosis of MA. Thus, we observed DA in 64 (77.3%) subjects of 82 patients with PTB and concomitant COPD and a history of severe allergic reactions. This supports the fact that before initiating treatment, careful assessment of the allergic history of patients with PTB and COPD should be done by phthisiologists and pulmonologists.

Based on the recommendations of Ukrainian pharmacovigilance experts, the clinical manifestations of DA should be differentiated according to their severity. 49% (69.0%) of 71 cases of DA observed in the subjects were recognized as mild (itching, acute urticaria, isolated eosinophilia, which usually disappear 3 days after the discontinuation of the allergy-causing drug and initiation of antihistamines). Moderate events (acute urticaria, Quincke edema, eczematous dermatitis, erythema multiforme, fever, poly- and monoarthritis, toxic-allergic myocarditis, which are more likely to be eliminated within 4–5 days after withdrawal of a suspected drug, but require the administration of antihistamines and systemic corticosteroids at average doses) were seen in 19 (26.8%) of 71 patients with PTB and concomitant COPD who experienced DA. Severe events (anaphylactic shock, Lyell's syndrome, severe damage to the internal organs, namely: myocarditis with heart rhythm disorders, nephrotic syndrome, etc., whose symptoms disappear within 7–10 days after the discontinuation of the allergy-causing drug and initiation of epinephrine, antihistamines, systemic corticosteroids and other medicines) were reported in 3 (4.2%) of 71 individuals with DA due to therapy of PTB and COPD.

The reactions of non-allergic (toxic) origin to ATA that occurred in 86 of the above 193 patients with adverse reactions to ATA were mainly manifested as the gastrointestinal, hepatobiliary, urogenital and nervous system disorders, which are typical for this group of drugs. Such adverse reactions and the tactics of their elimination are described in detail in the «Unified clinical protocol of primary, secondary (specialized) and tertiary (highly specialized) medical care for adults. Tuberculosis» (Order of the Ministry of Health of Ukraine 3620 of 04.09.2014). Since this was not the aim of our study, so we do not discuss this topic in detail.

Of course, as mentioned earlier [7–9], the main difficulties in the differentiating adverse reactions to both ATA and other drugs, concern toxic (which these authors also refer to the so-called false allergic reactions) and allergic drug reactions, so for this purpose, we used the criteria given in Table below.

Identification of allergy-causing drugs takes an important place in the diagnosis of DA. The data of the history of allergic disorders and the findings of laboratory testing with allergy-causing drugs allows to find out that the incidence of DA was higher with the use of the following ATA: isoniazid – 28.3%, pyrazinamide –23.9%, streptomycin – 22.5%, rifampicin – 9.9%, kanamycin – 9.9%, ethambutol –8.5%, ofloxacin – 8.5%, moxifloxacin – 4.2% cases.

Table

Differential and diagnostic signs of toxic, false allergic and allergic reactions to medicinal products

Signs	Adverse reactions		
	toxic	false allergic	allergic
Period of sensitization	No	No	Yes
Dose dependence	Yes	Yes	No
Dependence on the route of administration	Yes	Yes	No
Potential of occurrence due to the drugs having common antigenic determinants	No	No	Yes
Potential of recurrence	Not sure	Not sure	Sure
Signs suggesting pharmacological effect of the drug	Frequently	No	No
Clinical pattern similar to that of typical AD	No	Yes	Yes
Effect of antihistamines	No	Є	Є

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Interestingly, more than one ATA was identified as allergy-causing drugs in 11 (15.5%) of 71 patients with DA. Data regarding the spectrum of allergy-causing drugs are generally consistent with those of other investigators [1, 5–7] which also observed higher sensitizing properties of isoniazid, pyrazinamide and streptomycin and lower – of ethambutol, rifampicin, kanamycin, ofloxacin and moxifloxacin.

In order to properly choose the methods of diagnosis and treatment of DA, the distribution to 4 types of allergic reactions according to the classification of Jell and Coombs has traditionally been used [8]. Therefore, the treatment of patients with clinical manifestations of type 1 allergic reactions (anaphylactic shock, allergic rhinitis, shortness of breath, urticaria, isolated eosinophilia, etc.) was performed with the use of epinephrine, antihistamines, and, rarely, systemic glucocorticoids. Treatment of patients with type 2 DA (hemolytic anemia, leukopenia, agranulocytosis, pancytopenia) was performed based on the recommendations of the hematologist and more frequently included systemic glucocorticoids. Treatment of patients with clinical manifestations of type 3 allergic reactions (serum sickness, eczema, damage with the immune complexes of internal organs, exogenous allergic alveoli, Arthus-like reaction, anemia, agranulocytosis, vasculitis, etc.) was performed after consultation with the appropriate professionals according to the protocols for treatment of these diseases using systemic glucocorticoids and protease inhibitors. The treatment of patients with type 4 DA (contact dermatitis, photoallergic dermatitis, erythemovesicular dermatitis, hemorrhagic vasculitis, etc.) was performed after consultation with the dermatologist with frequent use of topical glucocorticoids. As a rule, for any type of DA, identification of allergy-causing drugs was followed by their elimination. It should be noted that as a result of such tactics of management of patients with DA, all of them succeeded to complete the main course of antimycobacterial therapy.

It was quite reasonable to expect that the adverse reactions to ATA both of allergic and toxic origin should affect the efficacy of treatment, significantly reducing it and prolonging the duration of chemotherapy in the respective patient populations. Thus, after 3 months of ATA chemotherapy, healing the cavities of lung destruction occurred in (46.8±8.6)% of subjects with PTB and concomitant COPD without adverse reactions to ATA and only in (26.5±3.8)% of patients, in which, besides the aforementioned conditions, adverse reactions to ATA were seen. Differences between the parameters are significant, at $p < 0.05$. Slow healing the cavities in the lungs of individuals with adverse reactions to ATA led to a longer stay in the hospital of the respective patient populations. Thus, in persons without adverse reactions to ATA, the average length of their stay in the hospital was (164.2± 6.0) bed-days, and in persons with complications during chemotherapy – (203.1±4.2) bed-days. Differences between the parameters are significant, at $p < 0.01$.

Consequently, the issue of adverse reactions to ATA, especially DA, in patients with a combination of PTB and COPD is relevant for allergy, phthisiology and pulmonology and requires further research.

Conclusions

Adverse reactions to ATA are often observed during therapy of patients with PTB and concomitant COPD, since they have been recorded in (58.3±2.9)% of the patients. Among them, DA observed in (21.5±2.1)% subjects of this patient population takes a special place.

In DA structure, mild (itching, acute urticaria, isolated eosinophilia,) and moderate (acute urticaria, Quincke edema, eczematous dermatitis, erythema multiforme, fever, poly- and monoarthritis, toxic-allergic myocarditis) allergic reactions are prevalent in individuals with PTB and COPD; and they are observed 69.0% and 26.8% cases, respectively.

In patients with PTB and COPD, isoniazid (28.3%), pyrazinamide (23.9%) and streptomycin (22.5%) cause DA more frequently, and rifampicin (9.9%), kanamycin (9.9%), ethambutol (8.5%), ofloxacin (8.5%) and moxifloxacin (4.2% cases) – rarely.

Development of adverse reactions to ATA affects the efficacy of treatment of patients with PTB and COPD, reducing the rate of healing the destruction of pulmonary parenchyma and prolonging the duration of their stay in the hospital.

Список літератури

1. Зайков, С.В. Частота, структура, можливості діагностики та профілактики медикаментозної алергії у хворих на туберкульоз дітей / С.В. Зайков, Л.М. Кириченко // Укр. пульмонол. журн. – 2005. – № 2. – С. 37–40.

2. Кужко, М.М. Ефективність лікування та профілактика алергічних ускладнень у хворих на туберкульоз легень / М.М. Кужко [та ін.] // Астма та алергія. – 2014. – № 1. – С. 30–34.

3. Кужко, М.М. Токсикоалергічні реакції у хворих на туберкульоз легень із супутніми хронічними обструктивними захворюваннями легень / М.М. Кужко [та ін.] // Астма та алергія. – 2006. – № 1. – С. 88.

4. Мамолат, А.С. Побочные реакции при антибактериальной терапии больных туберкулезом / А.С. Мамолат, Е.Ф. Чернушенко. – К.: Здоров'я, 1975. – 136 с.

5. Мишин, В.Ю. Частота, характер и диагностика побочных реакций у больных туберкулезом легких при химиотерапии

References

1. Zaykov SV, Kirichenko LM. Chastota, struktura, mozhlivosti diagnostiki ta profilaktiki medikamentoznoï alergiï u khvorikh na tuberkul'oz ditey (Frequency, structure, diagnostic possibilities and prevention of medical allergy in children with tuberculosis). Ukr. pul'monol. zhurn. 2005;2:37–40.

2. Kuzhko MM, et al. Efektivnist' likuvannya ta profilaktika alergichnikh uskladnen' u khvorikh na tuberkul'oz legen' (Effectiveness of treatment and prevention of allergic complications in patients with pulmonary tuberculosis). Astma ta alergiya. 2014;1:30–34.

3. Kuzhko MM, et al. Toksiko-alergichni reaktsiï u khvorikh na tuberkul'oz legen' iz suputnimi khronichnimi obstruktivnimi zakhvoryuvannyami legen' (Toxic and allergic reactions in patients with pulmonary tuberculosis with concomitant chronic obstructive pulmonary diseases). Astma ta alergiya. 2006;1:88.

4. Mamolat AS, Chernushenko EF. Pobochnye reaktsii pri antibakterial'noy terapii bol'nykh tuberkulezom (Adverse reactions with

ISSN 2307-3373

основными препаратами / В.Ю. Мишин [и др.] // Проблемы туберкулеза. – 2003. – № 7. – С. 24–29.

6. Пухлик, Б.М. Лекарственная аллергия у больных туберкулезом легких / Б.М. Пухлик [и др.] // Врачебное дело. – 1991. – № 4. – С. 76–78.

7. Пухлик, Б.М. Побічна дія лікарських засобів у фтизіатричній практиці / Б.М. Пухлик // Туберкульоз, легеневі хвороби, ВІЛінфекція. – 2011. – № 1 (04). – С. 20–27.

8. Пухлик, Б.М. Довідник з алергології / Б.М. Пухлик. – К.: ДокторМедіа, 2011. – 394 с.

9. Фещенко, Ю.І. Реєстрація побічних реакцій протитуберкульозних препаратів при лікуванні хворих на туберкульоз / Ю.І. Фещенко [та ін.] // Укр. пульмонол. журн. – 2008. – № 4. – С. 8–13.

10. Фещенко, Ю.І. Бронхіальна астма, хронічне обструктивне захворювання легень: перспективна глобальна стратегія ведення, новітні методи діагностики, сучасні підходи до терапії / Ю.І. Фещенко // Астма та алергія. – 2015. – № 4. – С. 36–42.

11. Фещенко, Ю.І. Особливості сучасної ситуації з туберкульозу в Україні / Ю.І. Фещенко [та ін.] // Укр. пульмонол. журн. – 2016. – № 1. – С. 5–9.

12. Ellertsen, L.K. Allergic sensitisation in tuberculosis patients at the time of diagnosis and following chemotherapy / L.K. Ellertsen [et al.] // BMC Infectious Diseases. – 2009. – N 9. – P. 100.

13. Global Atlas of Allergy // Published by the European Academy of Allergy anad Clinical Immunology, 2014. 388 p.

14. Reider, H. Interventiones fof tuberculosis control and elimination / H. Reider. – Paris, 2002. – P. 252.

antibacterial therapy of patients with tuberculosis). Kyiv: Zdorov'ya, 1975. 136 p.

5. Mishin VYu, et al. Chastota, kharakter i diagnostika pobochnykh reaktsiy u bol'nykh tuberkulezom legkikh pri khimioterapii osnovnymi preparatami (The frequency, nature and diagnosis of adverse reactions in patients with pulmonary tuberculosis in chemotherapy with basic drugs). Problemy tuberkuleza. 2003;7:24–29.

6. Pukhlik BM, et al. Lekarstvennaya allergiya u bol'nykh tuberkulezom legkikh (Drug allergy in patients with pulmonary tuberculosis). Vrachebnoe delo. 1991;4:76–78.

7. Pukhlik BM. Pobichna diya likars'kikh zasobiv u ftiziatrichniy praktitsi (Side effects of medicines in phthisiological practice). Tuberkul'oz, legenevi khvorobi, VIL-infektsiya. 2011;1(04):20–27.

8. Pukhlik BM. Dovidnik z alergologiï (Handbook of allergy). Kyiv: Doktor-Media, 2011. 394 p.

9. Feshchenko YuI, et al. Reestratsiya pobichnikh reaktsiy protituberkul'oznikh preparativ pri likuvanni khvorikh na tuberkul'oz (Registration of side effects of anti-TB drugs in the treatment of patients with tuberculosis). Ukr. pul'monol. zhurn. 2008;4:8–13.

10. Feshchenko YuI. Bronkhial'na astma, khronichne obstruktivne zakhvoryuvannya legen': perspektivna global'na strategiya vedennya, novitni metodi diagnostiki, suchasni pidkhodi do terapiï (Bronchial asthma, chronic obstructive pulmonary disease: promising global strategy of management, advanced diagnostic methods, modern approaches to therapy). Astma ta alergiya. 2015;4:36–42.

11. Feshchenko YuI, et al. Osoblivosti suchasnoï situatsiï z tuberkul'ozu v Ukraïni (Particularities of the situation in the Tuberculosis in Ukraine). Ukr. pul'monol. zhurn. 2016;1:5–9.

12. Ellertsen LK, et al. Allergic sensitisation in tuberculosis patients at the time of diagnosis and following chemotherapy. BMC Infectious Diseases. 2009;9:100.

13. Global Atlas of Allergy. Published by the European Academy of Allergy anad Clinical Immunology, 2014. 388 p.

14. Reider H. Interventiones fof tuberculosis control and elimination. Paris, 2002. P. 252.

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